AMENDMENTS TO THE SPECIFICATION

Please amend the paragraph beginning on page 9, line 12, as follows:

Further, it is preferred that the region from α2 to β2 in the protein corresponds to the sequence of the amino acid ~~numbers~~ residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the region from β3 to β4 corresponds to the sequence of the amino acid ~~numbers~~ residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1. In this embodiment, it is preferred that at least one acidic amino acid residue of which α carbon atom exists within 10 Å from the α carbon atom of the arginine residue of the amino acid ~~number~~ residue 103 in the amino acid sequence of SEQ ID NO: 1 is replaced with a neutral amino acid residue. Further, the acidic amino acid residue preferably is at least one residue selected from the aspartic acid residue of the amino acid ~~number~~ residue 54, the aspartic acid residue of the amino acid ~~number~~ residue 101 and the glutamic acid residue of the amino acid ~~number~~ residue 106 in the amino acid sequence of SEQ ID NO: 1.

Please amend the paragraph beginning on page 10, line 13, as follows:

The production method of the present invention preferably further comprises bonding a polyoxyalkylpolyol group to the protein. Preferably, the protein contains a cysteine residue corresponding to a cysteine residue of the amino acid ~~number~~ residue 81 in the amino acid sequence of SEQ ID NO: 1, and the polyoxyalkylpolyol group is bonded to this cysteine residue. The polyoxyalkylpolyol group is preferably a polyethylene glycol group.

Please amend the paragraph beginning on page 11, line 8, as follows:

(a) a protein, in which the region from α2 to β2 has the sequence of the amino acid ~~numbers~~ residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the region from β3 to β4 has the sequence of the amino acid ~~numbesr~~ residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1;

Please amend the paragraph beginning on page 11, line 13, as follows:

(b) the protein according to (a), in which substitution, insertion or deletion of one or several amino acid residues is included in the region from α2 to β2 having the sequence of the amino acid ~~numbers~~ residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and/or the region from β3 to β4 having the sequence of the amino acid ~~numbers~~ residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1.

Please amend the paragraph beginning on page 11, line 24, as follows:

(A) the amino acid sequence of the amino acid ~~numbers~~ residues 47 to 111 in the amino acid sequence of SEQ ID NO: 1;

Please amend the paragraph beginning on page 11, line 26, as follows:

(B) the amino acid sequence according to (A), in which the cysteine residue of the amino acid ~~number~~ residue 81 in the amino acid sequence of SEQ ID NO: 1 is replaced with an alanine residue.

Please amend the paragraph beginning on page 12, line 15, as follows:

The protein of the present invention preferably has a sequence in which at least one acidic amino acid residue of which α carbon atom exists within 10 Å from the α carbon atom of the arginine residue of the amino acid ~~number~~ residue 103 in the amino acid sequence of SEQ ID NO: 1 is replaced with a neutral amino acid residue. In this embodiment, it is preferred that the acidic amino acid residue to be replaced is composed of at least one residue selected from the aspartic acid residue of the amino acid ~~number~~ residue 54, the aspartic acid of the amino acid ~~number~~ residue 101 and the glutamic acid residue of the amino acid ~~number~~ residue 106 in the amino acid sequence of SEQ ID NO: 1.

Please amend the paragraph beginning on page 12, line 28, as follows:

Preferably, the protein of the present invention is bonded to a polyoxyalkylpolyol group. The protein of this embodiment preferably contains a cysteine residue corresponding to the cysteine residue of the amino acid ~~number~~ residue 81 in the amino acid sequence of SEQ ID NO: 1, and the polyoxyalkylpolyol group is bonded to this cysteine residue. The polyoxyalkylpolyol group is preferably a polyethylene glycol group.

Please amend the paragraph beginning on page 15, line 10, as follows:

The present invention will be described in detail below. In the following description, an amino acid residue may be referred to by using a three-letter code. When a numeral is added to the three-letter code, the numeral represents an amino acid ~~number~~ residue in the amino acid sequence of SEQ ID NO: 1, unless otherwise specified. When a three-letter code is further added, it means replacement with an amino acid residue of the further added three-

letter code (for example, "Cys81Ala" means that a cysteine residue of the amino acid ~~number~~ residue 81 in the amino acid sequence of SEQ ID NO: 1 is replaced with an alanine residue).

Please amend the paragraph beginning on page 22, line 19, as follows:

(A) an amino acid sequence of the amino acid ~~numbers~~ residues 47 to 111 in the amino acid sequence of SEQ ID NO: 1;

Please amend the paragraph beginning on page 22, line 21, as follows:

(B) the amino acid sequence according to (A), in which Cys of the amino acid ~~number~~ residue 81 in the amino acid sequence of SEQ ID NO: 1 is replaced with Ala.

Please amend the paragraph beginning on page 22, line 24, as follows:

In those proteins, the region from α2 to β2 is a region corresponding to the amino acid ~~numbers~~ residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the region from β3 to β4 is a region corresponding to the amino acid ~~numbers~~ residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1. In these proteins, an acidic amino acid residue having an α carbon atom within 10 Å from the α carbon atom in Arg of the amino acid ~~number~~ residue 103 in the amino acid sequence of SEQ ID NO: 1 is preferably replaced with a neutral amino acid residue. Alternatively, it is preferred that an acidic amino acid residue within amino acid ~~numbers~~ residues 47 to 59 and 100 to 106 in the amino acid sequence of SEQ ID NO: 1 is replaced with a neutral amino acid residue. Further, it is more preferred that the acidic amino acid residue is composed of one or more of residues selected from Asp of the amino acid ~~number~~ residue 54, Asp of the amino acid ~~number~~ residue 101 and Glu of the amino acid

~~number~~ residue 106 in the amino acid sequence of SEQ ID NO: 1. The distance between α carbons is determined by X-ray crystallography of the protein.

Please amend the paragraph beginning on page 28, line 9, as follows:

In this embodiment, it is preferred that the protein contains Cys corresponding to Cys of the amino acid ~~number~~ residue 81 in the amino acid sequence of SEQ ID NO: 1 and a polyoxyalkylpolyol group is bonded to this Cys. Further, in the case of a protein where the region containing the loop structure between β2 and β3 is replaced, if Cys is contained in the amino acid residue with which the loop structure is replaced, the polyoxyalkylpolyol group may be bonded to the Cys.

Please amend the paragraph beginning on page 34, line 28, as follows:

In the case of AS1051, a residue of the amino acid ~~number~~ residue 81 in the amino acid sequence of SEQ ID NO: 1 may be Ala or Cys in a protein before modification. Further, Met corresponding to the translation initiation point may be added to an amino terminus. Further, an improved AS1051 prepared by the aforementioned "removal of the loop structure region not involved in the glycoprotein Ib-binding activity" can also be used.

Please amend the paragraph beginning on page 35, line 19, as follows:

More specifically, examples of the protein of the present invention include AS1051 having the amino acid sequence of SEQ ID NO: 1, such a protein in which its Cys81 is replaced with Ala and a protein wherein a part of the amino acid sequence is removed as in the above example, for example, the aforementioned AS1051-G4, in which one or more

amino acid residues of Asp54, Asp101 and Glu106 (numerals are amino acid ~~numbers~~ residues corresponding to those in SEQ ID NO: 1 and, in a protein obtained by modifying a part of SEQ ID NO: 1, numerals are amino acid ~~numbers~~ residues parallerized in consideration to the change of an amino acid ~~number~~ residue ) are replaced, i.e., Asp is replaced with one of amino acids having different characteristics such as Ala, Ser and Asn, and Glu is replaced with one of amino acids having different characteristics such as Ala, Ser and Gln.

Please amend the paragraph beginning on page 58, line 17, as follows:

Proteins were prepared in which amino acids of AS1051-G4 prepared in Example 2 were mutated as shown in Table 1. The amino acid ~~numbers~~ residues used in the table correspond to the amino acid ~~numbers~~ residues in SEQ ID NO: 1.

Please amend the paragraph beginning on page 64, line 5, as follows:

Proteins containing a plurality of amino acid mutations were prepared in the same manner as in the method for preparing the proteins containing a single amino acid mutation. Designations of mutant genes and their mutations are shown in Table 3. The amino acid ~~numbers~~ residues used in the table correspond to the amino acid ~~numbers~~ residues in SEQ ID NO: 1.

Please amend the paragraph beginning on page 71, line 13, as follows:

Subsequently, the polyethylene glycol-bonding position in AS1051-PEG5000 and linkage scheme of disulfide bonds in the other Cys residues were determined as follows.

AS1051-PEG5000 (100 μg) was digested with lysyl endopeptidase (5 μg, Wako Pure Chemical Industries) in 0.1 M Tris-HCl buffer (pH 8.5) containing 2 mM EDTA at 37°C for 5 hours and fractionated by high performance liquid chromatography using a reverse phase column (Vydac 218TP54, Vydac). Elution was performed with a linear gradient of water/acetonitrile containing 0.1% trifluoroacetic acid (TFA) (acetonitrile concentration of from 0 to 50% for 10 minutes, acetonitrile concentration of from 50% to 100% for 5 minutes). Thus, peptide chains obtained by digestion were obtained as Peaks 1 to 6 (FIG. 3). The amino acid sequence of each peptide chain was analyzed by using a protein sequencer Model 476A (Applied Biosystems). Since two Cys residues were contained in the chain of Peak 3, it was concluded that these two Cys residues were coupled to form a disulfide bond. Further, it was concluded that Peak 5 was composed of total three peptide chains, wherein two peptide chains containing one Cys residue and one peptide chain containing two Cys residues were coupled through disulfide bonds. The peptide chains of this Peak 5 were further digested with V8 protease (5 μg, Wako Pure Chemical Industries) in 10 mM ammonium carbonate buffer at 25°C for 24 hours and fractionated by high performance liquid chromatography using a reverse phase column (Pegasil ODS-II, Senshu Kagaku). Elution was performed with a linear gradient of water/acetonitrile containing 0.1% TFA (acetonitrile concentration of from 0 to 50% for 20 minutes). Thus, peptide chains obtained by digestion were prepared and their amino acid sequences were analyzed. As a result, it was confirmed that the polyethylene glycol chain was bonded to a Cys residue corresponding to the amino acid ~~number~~ residue 81 in SEQ ID NO: 1 and all the peaks supported that the peptides of Peak 5 had such a disulfide bond as shown in FIG. 3. The bonding scheme of disulfide bond

in AS1051-PEG determined as described above was the same as in the reported AS1051 (N. Fukuchi et al., WO95/08573) or other similar proteins originating from snake venom.